

Effects of Nasal Continuous Positive Airway Pressure on Awake Ventilatory Responses to Hypoxia and Hypercapnia in Patients with Obstructive Sleep Apnea

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TUN, Y., HIDA, W., OKABE, S., KIKUCHI, Y., KUROSAWA, H., TABATA, M. and SHIRATO, K. *Effects of Nasal Continuous Positive Airway Pressure on Awake Ventilatory Responses to Hypoxia and Hypercapnia in Patients with Obstructive Sleep Apnea.* Tohoku J. Exp. Med., 2000, **190** (2), 157-168 — This study was aimed to examine the short- and long-term effects of nasal continuous positive airway pressure (CPAP) on the chemosensitivity to hypoxia and hypercapnia in the patients with obstructive sleep apnea (OSA). Awake ventilatory responses to hypoxia and hypercapnia were examined in 28 patients (3 female) with moderate to severe OSA. All these tests were examined before and after 2 weeks of nasal CPAP. In 10 patients these tests were repeated after 3-6 months of nasal CPAP. All were also tested for spirometry and arterial blood gas analysis. Patients were middle-aged (48.9 ± 9.9 years) and their mean apnea-hypopnea index was 58.3 ± 20.4 /hour. After 2 week of nasal CPAP, PaO_2 significantly increased (77.7 ± 11.8 vs. 84.6 ± 9.8 mmHg) and PaCO_2 significantly decreased (44.9 ± 3.8 vs. 42.3 ± 3.7 mmHg). The ventilatory response to hypoxia significantly decreased (0.80 ± 0.51 vs. 0.61 ± 0.51 liter/min/%) whereas the ventilatory response to hypercapnia significantly increased after 2 weeks (1.47 ± 0.73 vs. 1.80 ± 0.76 liter/min/mmHg). Similar findings were also observed after 3-6 months of nasal CPAP in 10 OSA patients. Nasal CPAP treatment can alter the ventilatory responses in patients with OSA. ——— ventilatory responses; nasal continuous positive airway pressure; obstructive sleep apnea © 2000 Tohoku University Medical Press

Obstructive sleep apnea (OSA) is now well recognized by its repeated episodes of upper airway occlusion during sleep. These recurrent cessations of airflow are associated with transient episodes of hypoxia, hypercapnia, and increasing inspiratory effort against the obstructed upper airway, all of which

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finally lead to a brief arousal and restoration of airway patency and blood gases (Guilleminault et al. 1986). It is possible that these repeated episodes of nocturnal hypoxia and hypercapnia affect ventilatory control in the patients with OSA. In addition, instability in ventilatory control such as an inappropriate ventilatory response to hypoxia, hypercapnia, or metabolic acidosis, has been suspected to be a cause of the pathogenesis in sleep disordered breathing (Zwillich et al. 1975; Longobardo et al. 1982).

The hypoxic ventilatory response is still a subject of debate in OSA. Concerning the hypoxic ventilatory response in patients with OSA, there are relatively few data and inconsistent findings. Previously it was reported that there was a low (Lin 1994) or normal (Rapoport et al. 1986; Gold et al. 1993) ventilatory response to hypoxia in patients with OSA. After nasal continuous positive airway pressure (CPAP) treatment the hypoxic ventilatory response increased (Lin 1994) or was not changed (Rapoport et al. 1986) in hypercapnic patients with OSA. Recently it has been reported that the hypoxic ventilatory response was enhanced in patients with OSA (Hedner et al. 1992; Narkiewicz et al. 1999). By eliminating repeated nocturnal hypoxic events, the ventilatory response to hypoxia could be modified after nasal CPAP treatment.

There are also conflicting findings concerning the ventilatory response to hypercapnia in patients with OSA. The ventilatory response to hypercapnia was decreased (Garay et al. 1981; Lopata et al. 1982; Gold et al. 1993), increased (Verbraeche et al. 1995) or normal (Garay et al. 1981) in OSA patients. Again, there are inconsistent outcomes regarding the ventilatory response to hypercapnia after nasal CPAP treatment. A reversible increase in the ventilatory response to hypercapnia was found in patients with OSA after treatment (Berthon-Jones and Sullivan 1987; Lin 1994), while the response was not changed in another study (Verbraeche et al. 1995).

It is now well recognized that treatment by nasal CPAP for patients with OSA effectively eliminates obstructive apneas and hypopneas, resulting in an improvement of daytime sleepiness (Taguchi et al. 1997) and overall sleep symptomatology (Sullivan et al. 1981). Therefore, it is reasonable to expect that nasal CPAP treatment can alter the ventilatory response to the chemical stimuli in patients with OSA. Clarifying these responses we will increase our understanding of the pathophysiology of OSA. Clarifying these responses we will increase our understanding of the pathophysiology of OSA. But, the previous findings of the ventilatory responses to hypoxia and hypercapnia were inconsistent since most of studies performed in a small group of patients and short-term observations after nasal CPAP treatment. Therefore, we had done these ventilatory tests to hypoxia and hypercapnia in a relatively large group of patients with OSA and followed the effects of treatment in short and long periods.

This study was aimed to examine the ventilatory responses to hypoxia and hypercapnia before, after 2 weeks and after 3–6 months of nasal CPAP treatment

in patients with OSA.

METHODS

Subjects

We recruited 28 consecutive patients (3 female) with moderate to severe OSA who had a history of habitual snoring and excessive daytime sleepiness. They were newly diagnosed as OSA and had never been treated with nasal CPAP or by any other treatment for sleep apnea previously. Patients with major medical illness such as severe heart failure, neurological disorders, uncontrolled diabetes mellitus were excluded from this study. The Epworth sleepiness scale (Johns 1991) scored daytime sleepiness. Each patient gave informed consent to the protocol, which was approved by the Human Research Committee of our institute.

Overnight sleep study and nasal CPAP titration

An overnight sleep study was carried out in a darkened quiet room using standard polysomnographic equipment in a manner similar to that in the previous study (Okabe et al. 1995). Briefly, electroencephalography (C4/A1, C3/A2), electrooculography, submental electromyography and electrocardiography with surface electrodes, air flow at the nose and mouth with thermistors, respiratory movements of the rib cage and abdomen with inductive plethysmography (Respirace; Ambulatory Monitoring Inc., Ardsley, NY, USA) and percutaneous arterial oxygen saturation (SaO_2) with a finger pulse oximeter (Biox 3700, Ohmeda, Boulder, CO, USA) were simultaneously measured. All variables were recorded on an 8-channel thermal chart recorder (model 360, NEC San-ei, Tokyo) together with a personal computer using MacLab with a chart 3.5 system (115-120/VAC, Kipping, Australia).

Apnea is defined as a cessation of airflow lasting 10 seconds or more, while hypopnea is defined as more than a 50% decrease in thoracoabdominal amplitude (Respirace signal) associated with a decline in SaO_2 of more than 4% from the preceding value (Gould et al. 1986). The apnea-hypopnea index (AHI) was calculated according to the definition of Guilleminault and associates (Guilleminault et al. 1986). Sleep stages were determined according to international standard criteria (Rechtschaffen and Kales 1968).

Nasal CPAP titration was performed under standard polysomnography on the following day after the diagnostic polysomnography. The pressure with which the patients continued to use nasal CPAP was determined on the titration night. All patients in this study were hospitalized for 2 weeks and managed with a supervised program including dietary therapy.

Spirometry and arterial blood gas analysis

Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured with a rolling-seal spirometry (Fudac-70s, Fukuda, Tokyo).

A 2-ml arterial blood sample was taken, and blood gas analysis including arterial oxygen tension (PaO_2), arterial carbon dioxide tension (PaCO_2), and pH was performed with a pH/blood gas analyzer (Model 213; Instrumentation Laboratories, Lexington, MA, USA) at 30 minutes before spirometry. These spirometry and arterial blood gas analysis were done in patients with sitting position and at the same day of the ventilatory tests.

Ventilatory responses to hypoxia and hypercapnia

All patients were tested for ventilatory responses to hypoxia and hypercapnia before and two weeks after the nasal CPAP treatment. Ten patients continued to be followed for these two tests after 3–6 months of nasal CPAP treatment. All measurements were performed with the patients in a sitting position at 2–3 p.m. to control for diurnal variations in the ventilatory response. Before each test they had been resting for at least 20 minutes to ensure stable breathing. On that day, they refrained from coffee, smoking and alcohol before the tests. During these tests the patients were kept alert by being warned verbally not to fall asleep.

The ventilatory responses to hypoxia and hypercapnia were measured using the method of Rebuck and Campbell (1973) and Read (1967), respectively. During the test the patient, wearing a nose clip, was allowed to breathe through the mouthpiece, which was connected to a unidirectional respiratory valve (model 1900, Han Rudolph, Kansas, MO, USA) and a rebreathing circuit. The resistance of the circuit was $0.9 \text{ cmH}_2\text{O/liter/second}$ and linear to 3 liter/second. From the unidirectional respiratory valve, the end-tidal oxygen tension (PETO_2) and carbon dioxide tension (PETCO_2) were measured continuously with a mass spectrometer (WSMR-1400, Westron, Chiba). Arterial oxygen saturation was monitored continuously with a finger pulse oximeter. Minute ventilation (V_E) obtained by the electrically integrated expiratory flow signal was recorded using a Fleisch pneumotachography (No. 3, Chest Corp., Tokyo). During the isocapnic hypoxic test, a bypass circuit consisting of a carbon dioxide absorber and a variable fan were connected between the inspiratory and expiratory lines to maintain the end-tidal carbon dioxide tension at the value of resting control breathing. In the hypoxic test resting PETCO_2 after nasal CPAP was also maintained at a similar level to that before nasal CPAP.

The patients breathed room air through the mouthpiece while wearing a nose clip for 2–3 minutes. After the adaptation, i.e., the stabilization of minute ventilation and PETCO_2 , room air was switched to breathing through a bag containing a constant volume (VC plus one liter) of a predetermined gas mixture of 21% O_2 in N_2 for the response to hypoxia and 7% CO_2 in 93% O_2 for the response to hypercapnia, respectively. These tests were stopped when the patient reached to 9% PETCO_2 and 75% SaO_2 . The ventilatory responses to hypoxia and hypercapnia were expressed as the slope of the regression line of ventilation against SaO_2 ($\Delta \text{V}_\text{E} / \Delta \text{SaO}_2$) and the end-tidal CO_2 ($\Delta \text{V}_\text{E} / \Delta \text{PETCO}_2$), respectively.

Statistics

All data were expressed as means \pm s.d. unless otherwise mentioned. Among data before and after 2 weeks or 3–6 months of nasal CPAP, two-way analysis of variance (ANOVA) was done and if significant, a paired *t*-test was used as post hoc test. To compare normocapnic and hypercapnic groups, an unpaired *t*-test was applied. The relation between the change in ventilatory response and the changes in other parameters after nasal CPAP was examined by using the Pearson correlation test. A two-tailed *p* value < 0.05 was considered significant.

RESULTS

Characteristics of patients with OSA

The characteristics of the patients before and after nasal CPAP (2 weeks) are shown in Table 1. The mean age for patients was 48.4 ± 9.9 year. They had daytime sleepiness at an Epworth sleepiness scale of 16.3 ± 4.8 . None of the patients had apparent obstructive airway disease. They were moderate to severe OSA with a mean AHI of 58.3 episodes/hour ranging from 78.7 to 37.9. The

TABLE 1. *Characteristics of patients with OSA before and after NCPAP (2 weeks) treatment (n = 28)*

	Before NCPAP	After NCPAP	<i>p</i> -Value
Age (year)	48.4 ± 9.9		
Sex (m/f)	25/3		
Height (cm)	164.1 ± 7.8		
Body weight (kg)	82.7 ± 19.2	80.7 ± 18.7	0.01
Body mass index (kg/m ²)	30.5 ± 5.8	29.8 ± 5.4	0.01
Epworth Sleepiness Scale (ESS)	16.3 ± 4.8	5.0 ± 4.4	0.001
VC (liter)	3.8 ± 0.9	3.8 ± 0.9	n.s.
%VC (% of predicted value)	97.4 ± 15.2	97.0 ± 12.5	n.s.
FEV ₁ (liter)	3.0 ± 0.8	3.0 ± 0.8	n.s.
%FEV ₁ (% of predicted value)	96.6 ± 15.2	97.6 ± 15.7	n.s.
FEV ₁ /VC (%)	79.3 ± 7.7	80.3 ± 6.8	n.s.
PaO ₂ (mmHg)	77.7 ± 11.8	84.6 ± 9.8	0.01
PaCO ₂ (mmHg)	44.9 ± 3.8	42.3 ± 3.7	0.01
pH	7.39 ± 0.03	7.40 ± 0.02	n.s.
Apnea-hypopnea index (/hour)	58.3 ± 20.4	3.7 ± 4.4	0.001
Lowest SaO ₂ (%)	50.6 ± 16.2	85.2 ± 7.2	0.001
$\Delta V_E / \Delta \text{SaO}_2$ (liter/min/%)	0.80 ± 0.51	0.61 ± 0.51	0.01
$\Delta V_E / \Delta \text{PETCO}_2$ (liter/min/mmHg)	1.47 ± 0.73	1.80 ± 0.76	0.01

NCPAP, nasal continuous positive airway pressure; VC, slow vital capacity; FEV₁, forced vital capacity in one second; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; SaO₂, percutaneous arterial oxygen saturation; PETCO₂, end-tidal carbon dioxide tension. Values are means \pm s.d.

patients had lost weight significantly 2 weeks after nasal CPAP. The daytime sleepiness of patients was decreased after nasal CPAP treatment as the Epworth sleepiness scale decreased. After nasal CPAP, PaO_2 was increased and PaCO_2 was decreased significantly. The decreased AHI and improved lowest SaO_2 during sleep indicated the effectiveness of the nasal CPAP.

In the 10 patients with long-term nasal CPAP treatment, the body mass index was reduced (30.5 ± 6.2 vs. 29.1 ± 5.5 kg/m^2 , $p < 0.01$), PaO_2 was increased (77.7 ± 11.4 vs. 85.7 ± 7.1 mmHg , $p < 0.05$), and PaCO_2 was decreased (44.5 ± 2.5 vs. 42.1 ± 1.9 mmHg , $p < 0.05$) after 3–6 months when compared to the value of before nasal CPAP treatment.

Ventilatory response to hypoxia

The slope of the hypoxic ventilatory response was decreased significantly after 2 weeks of nasal CPAP treatment (Table 1). The decrease in the slope of the hypoxic test was still apparent after 3–6 months of nasal CPAP treatment (Fig. 1A). In the hypoxic test the minute ventilation at 80% SaO_2 was decreased after nasal CPAP treatment although it was not significant (21.4 ± 9.6 vs. 19.9 ± 2.6 liter/min , n.s.).

Ventilatory response to hypercapnia

The slopes of the hypercapnic ventilatory response were increased significantly after 2 weeks of nasal CPAP treatment (Table 1). The increase in the slope of the hypercapnic test was still apparent after 3–6 months of nasal

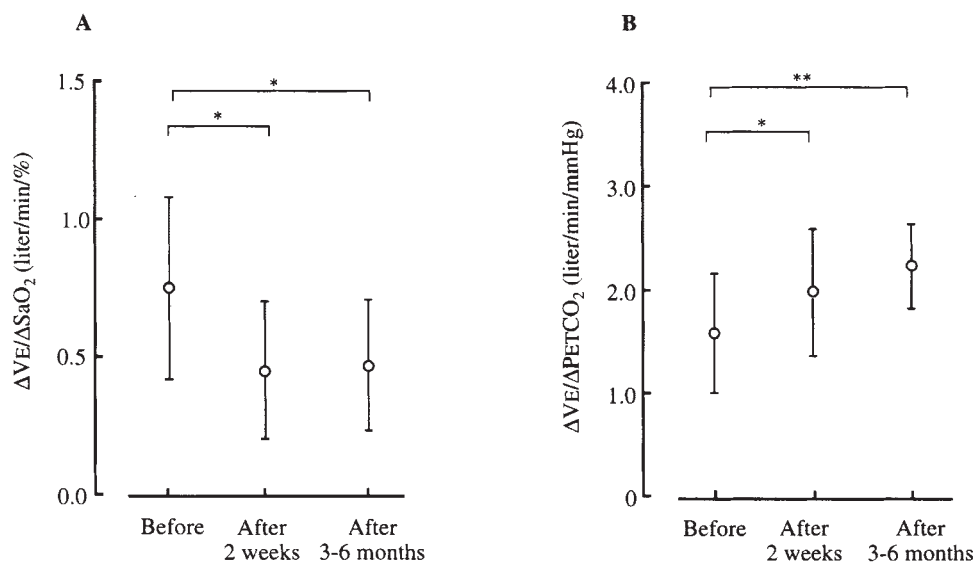


Fig. 1. Comparisons of awake ventilatory responses to hypoxia (A) and hypercapnia (B) among before, after (2 weeks) and after (3–6 months) of treatment in 10 patients with long-term nasal CPAP use. The decrease in the hypoxic ventilatory responses and the increase in the hypercapnic ventilatory responses were found after short- and long-term nasal CPAP treatment. Means \pm s.d. * $p < 0.05$. ** $p < 0.01$.

CPAP treatment (Fig. 1B). In the hypercapnic test the minute ventilation at $P_{ET}CO_2$ 60 mmHg was raised significantly after treatment (28.2 ± 12.0 vs. 33.1 ± 11.4 liter/min, $p < 0.001$), similar to the slope.

Normocapnic vs. hypercapnic groups

Patients were again divided into two groups: normocapnic and hypercapnic patients. Normocapnic OSA patients were defined as those with daytime arterial $PaCO_2 \leq 45$ mmHg whereas hypercapnic OSA patients were defined as those with daytime arterial $PaCO_2 > 45$ mmHg. The characteristics and changes before and after (2 weeks) nasal CPAP treatment in the normocapnic and hypercapnic groups are shown in Table 2. The hypercapnic group of patients with OSA had higher body mass indices than the normocapnic group and both groups showed a reduction in body mass indices 2 weeks after treatment. There were no significant differences in lung function before treatment. The hypercapnic group had low daytime PaO_2 and the lowest SaO_2 during sleep before treatment. Moreover, the AHI of this group was greater than that of the normocapnic group before treatment. The slope of the hypoxic ventilatory test was decreased in the hypercapnic group before treatment although not significantly.

In the hypercapnic group, the decrease in arterial $PaCO_2$ was significantly correlated with the increase in the slope of the hypercapnic ventilatory response

TABLE 2. Comparisons between normocapnic and hypercapnic groups of patients with OSA before and after NCPAP (2 weeks) treatment

	Normocapnic group (n = 18)		Hypercapnic group (n = 10)	
	Before NCPAP	After NCPAP	Before NCPAP	After NCPAP
Age (year)	46.8 ± 7.2		51.2 ± 13.4	
Body mass index (kg/m ²)	29.2 ± 4.6	28.7 ± 4.6^a	32.9 ± 7.2^b	31.7 ± 6.5^a
VC (liter)	3.9 ± 0.6	3.9 ± 0.5	3.4 ± 1.3	3.5 ± 1.2
VC (% of predicted value)	97.9 ± 15.8	96.7 ± 11.6	96.5 ± 14.6	97.3 ± 14.6
FEV ₁ (liter)	3.1 ± 0.4	3.1 ± 0.5	2.8 ± 1.2	2.8 ± 1.1
FEV ₁ (% of predicted value)	98.4 ± 11.8	98.8 ± 12.8	80.0 ± 8.2	80.7 ± 7.9
PaO_2 (mmHg)	82.4 ± 9.3	87.2 ± 8.4^a	69.1 ± 11.2^c	78.8 ± 10.8^a
$PaCO_2$ (mmHg)	42.6 ± 2.2	41.1 ± 3.4	48.9 ± 2.7^c	44.4 ± 3.4^b
pH	7.40 ± 0.03	7.40 ± 0.02	7.38 ± 0.03	7.40 ± 0.03^a
Apnea-hypopnea index (/hour)	51.1 ± 19.4	2.7 ± 2.3^b	71.3 ± 15.8^c	5.4 ± 6.5^b
Lowest SaO_2 (%)	55.9 ± 16.1	87.8 ± 4.9^b	41.2 ± 12.2^c	82.1 ± 9.3^b
$\Delta V_E / \Delta SaO_2$ (liter/min/%)	0.9 ± 0.4	0.7 ± 0.5^a	0.7 ± 0.6	0.5 ± 0.6^a
$\Delta V_E / \Delta P_{ET}CO_2$ (liter/min/mmHg)	1.7 ± 0.7	2.1 ± 0.5^a	1.0 ± 0.7^c	1.4 ± 0.9^a

Values are means \pm S.D.

^avs. before $p < 0.05$. ^bvs. before $p < 0.005$. ^cvs. normocapnic $p < 0.05$.

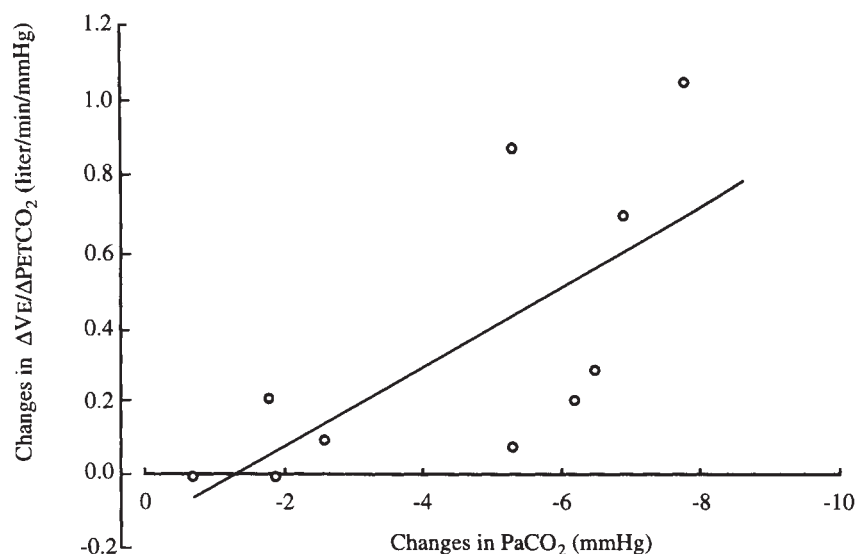


Fig. 2. Correlation of the decrease in PaCO₂ and the increase in the slope of the hypercapnic ventilatory response in hypercapnic patients while awake with obstructive sleep apnea after 2 weeks of nasal CPAP treatment. There was a significant correlation between these two parameters by the Pearson's correlation method ($n=10$; $r=0.64$; $p<0.05$). Line denotes regression line.

after 2 weeks of nasal CPAP treatment (Fig. 2), but such a correlation was not seen in the normocapnic group after nasal CPAP.

DISCUSSION

The main findings in this study are the following: (1) The hypoxic ventilatory response was decreased after 2 weeks as well as after 3–6 months of nasal CPAP. (2) The hypercapnic ventilatory response was increased after 2 weeks as well as after 3–6 months of nasal CPAP. In the hypercapnic group the decrease in arterial PaCO₂ was significantly correlated with the increase in the ventilatory response to hypercapnia.

The hypoxic ventilatory responses of these patients were found to be higher than the normal value of our laboratory (0.6 ± 0.3 liter/min/%O₂) and were decreased after nasal CPAP treatment. The normal values of the hypoxic ventilatory response were derived from 16 normal healthy subjects (14 male, 2 female) with mean age of 46.3 ± 15.5 years and mean body mass index of 25.9 ± 4.4 kg/m². The increased hypoxic ventilatory response before nasal CPAP is compatible with previous findings (Hedner et al. 1992; Narkiewicz et al. 1999). Our finding of increased hypoxic ventilatory responses in OSA patients before nasal CPAP was at variant with the previous studies (Zwillich et al. 1975; Rapoport et al. 1986) where they found low hypoxic ventilatory responses in OSA patients. The difference could be explained by the extent of daytime hypoxemia since their patients had more hypoxemia in daytime than our patients. Furthermore, we have found a reversible decrease in the hypoxic ventilatory responses in patients with OSA after nasal CPAP, a new finding of this study.

The exact mechanism of the enhanced hypoxic ventilatory response in OSA before nasal CPAP treatment is not well understood. But this increased hypoxic ventilatory response may be closely related to the events of nocturnal desaturation. In recent years, it is increasingly evident that the hypoxic ventilatory response might be related to the specific stimuli by which it is elicited such as the pattern, duration and intensity of exposure to hypoxia (Powell et al. 1998). A unique ventilatory acclimatization to short term hypoxia can be seen in humans and it requires a longer time course than in most other species. This is evident in one study reporting that six normal subjects at sea level showed biphasic ventilatory acclimatization to short term hypoxia at a high altitude of 4300 meters. After 5 days of hypoxic depression, they experienced an increase in the ventilatory response to hypoxia (Bisgard and Neubauer 1995). This adaptive phenomenon may likely be involved in the enhanced hypoxic ventilatory response to the nocturnal hypoxic episodes in patients with OSA. Another possibility is that there is an increase in ventilation following intermittent episodes of hypoxia, which lasts for minutes to several hours after the final episode of hypoxia (Powell et al. 1998). This so-called long-term facilitation has been observed in sleeping humans with snoring (Babcock and Badr 1998). This long-term facilitation involves cell bodies of serotonergic neurons located in brain stem raphe. These raphe neurons link to the spinal cord and cranial motor nuclei. Thus, a stimulation of these raphe neurons by a hypoxic episode has the potential to augment respiratory motor neuron excitability; thereby enhancing respiratory motor output (Powell et al. 1998). It could be speculated that the episodic desaturation during sleep would predispose patients with OSA to be more sensitive to hypoxic stimuli, thus enhancing the ventilatory responses to hypoxia. After nasal CPAP treatment, the elimination of the apnea-related nocturnal desaturation might reset the hypoxic sensitivity to a normal level. Previous studies reported that prolonged exposure to hypoxaemia was found to depress the hypoxic ventilatory response (Weil et al. 1971; Zwillich et al. 1975). But our patients had no gross daytime hypoxaemia (Table 1) and thus their hypoxic responses could not be depressed.

On the other hand, the change in the end-tidal CO_2 levels during the experiment periods as well as that level before and after nasal CPAP treatment should be considered. While testing the hypoxic response, decreasing end tidal CO_2 due to hyperventilation reduces the response and an uncontrolled increase in end-tidal CO_2 raises the ventilatory response to hypoxia (Moore et al. 1982). It is well established that hypocapnia diminishes greatly the carotid body hypoxic stimulation (Daristole et al. 1987). From the beginning, we were aware of this fact and maintained end-tidal CO_2 during the hypoxic test at the same level as the resting breathing state. Moreover, in the hypoxic tests after nasal CPAP the end-tidal CO_2 was adjusted to the same level as that of the hypoxic test before nasal CPAP. The finding of a decrease in the hypoxic response after nasal CPAP might not be

due to the change in the end tidal CO_2 during the hypoxic response tests. Therefore, we believe that the increased hypoxic response and its return to the normal level after nasal CPAP are substantial in patients with OSA.

The increase in the hypercapnic ventilatory response in the hypercapnic OSA patients after nasal CPAP treatment is consistent with previous findings (Berthon-Jones and Sullivan 1987; Lin 1994). In addition, we have found the increase in the hypercapnic ventilatory response in normocapnic OSA patients after nasal CPAP treatment. But the increase in the response after treatment in normocapnic patients with OSA is at variance with an other study (Lin 1994). This discrepancy may be due to a difference in disease severity of the patients studied and to a wide range of individual variations.

Before nasal CPAP treatment the mean of the group was found to be lower than the normal mean of the hypercapnic ventilatory response of our lab (1.80 ± 0.6 liter/min/mmHg) and returned to near the normal mean with nasal CPAP treatment. The normal values of the hypercapnic ventilatory response were derived from the same group mentioned above. We have found an increase in the response not only in hypercapnic patients but also in normocapnic patients with OSA after nasal CPAP. There are four possible mechanisms assumed to be responsible for the increase in the hypercapnic ventilatory response after nasal CPAP treatment. The first possibility is the reduction of the daytime sleepiness after nasal CPAP treatment, which might underlie the increase in the hypercapnic ventilatory response. One study (Cooper and Phillips 1982) reported that 15 normal subjects showed a 20% decrease in the ventilatory response to hypercapnia after two nights sleep deprivation. In patients with OSA the daytime sleepiness depresses the hypercapnic ventilatory response. By nasal CPAP treatment, the daytime sleepiness is reduced and this may have raised the hypercapnic ventilatory response. Secondly, the reduction in arterial carbon dioxide tension would elevate the ventilatory response to hypercapnia. This possibility could not be denied since we found that the change in the hypercapnic ventilatory response in the hypercapnic group was correlated significantly with the change in arterial carbon dioxide tension after nasal CPAP treatment (Fig. 2). The third possibility is that an improvement in lung mechanics could account for the increase in the response to hypercapnia. But this mechanism could not play a major role in our patients because there was no significant change in VC and FEV_1 after nasal CPAP in this study. Finally, it could be considered that the reduction of body weight might affect the ventilatory response to hypercapnia. In our study patients showed a reduction in body weight after 2 weeks of hospitalized management including dietary supervision. Although this reduction was statistically significant, the decrease in body weight was 2 kg in mean value (Table 1). One study reported no significant change in the slope of the hypercapnic ventilatory response in 4 obese women who underwent ileal bypass surgery for weight reduction (Kronenberg et al. 1975). Thus, body weight loss alone could not account for

the increase in the slope of the hypercapnic ventilatory response.

It was surprising that the changes in directions of the hypoxic ventilatory response and the hypercapnic ventilatory response after nasal CPAP were not same in our patients. It should be noticed that these ventilatory tests to hypoxia and hypercapnia are designed to evaluate separately the functions of peripheral and central chemoreceptors. For this reason the functions of peripheral and central chemoreceptors may be modified by OSA activities in a different way. This phenomenon has been observed in other studies (Gold et al. 1993; Narkiewicz et al. 1999).

In conclusion, OSA modifies the ventilatory responses to hypoxia and hypercapnia during the daytime. By short- and long-term nasal CPAP treatment the altered ventilatory responses can be reversed in these patients with OSA.

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References

- 1) Babcock, M.A. & Badr, M.S. (1998) Long-term facilitation of ventilation in humans during NREM sleep. *Sleep*, **21**, 709–716.
- 2) Berthon-Jones, M. & Sullivan, C.E. (1987) Time course of change in ventilatory response to CO₂ with long term CPAP therapy for obstructive sleep apnea. *Am. Rev. Respir. Dis.*, **135**, 144–147.
- 3) Bisgard, G.E. & Neubauer, J.A. (1995) Peripheral and central effects of hypoxia. In: *Regulation of Breathing*, 2nd ed., edited by J.A. Dempsey & A.I. Pack, Marcel Dekker, Inc., New York, pp. 617–668.
- 4) Cooper, K.R. & Phillips, B.A. (1982) Effect of short-term sleep loss on breathing. *J. Appl. Physiol.*, **53**, 855–858.
- 5) Daristotle, L., Berssenbrugge, A.D. & Bisgard, G.E. (1987) Hypoxic-hypercapnic ventilatory interaction at the carotid body of awake goats. *Respir. Physiol.*, **70**, 63–72.
- 6) Garay, S.M., Rapoport, D., Sorkin, B., Epstein, H., Feinberg, I. & Goldring, R.M. (1981) Regulation of ventilation in the obstructive sleep apnea syndrome. *Am. Rev. Respir. Dis.*, **124**, 451–457.
- 7) Gold, A.R., Schwartz, A.R., Wise, R.A. & Smith, P.L. (1993) Pulmonary function and respiratory chemosensitivity in moderately obese patients with sleep apnea. *Chest*, **103**, 1325–1329.
- 8) Gould, G.A., Whyte, K.F., Rhind, G.B., Airlie, M.A.A., Catterall, J.R., Shapiro, C.M. & Douglas, N.J. (1986) The sleep hypopnea syndrome. *Am. Rev. Respir. Dis.*, **137**, 895–898.
- 9) Guilleminault, C., Tilkian, A. & Dement, W.C. (1986) The sleep apnea syndromes. *Annu. Rev. Med.*, **27**, 465–484.
- 10) Hedner, J.A., Wilcox, I., Laks, L., Grustein, R.R. & Sullivan, C.E. (1992) A specific and potent pressor effect of hypoxia in patients with obstructive sleep apnea. *Am. Rev. Respir. Dis.*, **146**, 1240–1245.
- 11) Johns, M.W. (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, **14**, 540–545.

- 12) Kronenberg, R.S., Gabel, R.A. & Severinghaus, J.W. (1975) Normal chemoreceptor function in obesity before and after ileal bypass surgery to force weight reduction. *Am. J. Med.*, **59**, 349-352.
 - 13) Lin, C.-C. (1994) Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnea syndrome. *Eur. Respir. J.*, **7**, 2005-2010.
 - 14) Longobardo, G.S., Gothe, B. & Goldman, M.D. (1982) Sleep apnea considered as a control system instability. *Respir. Physiol.*, **50**, 311-333.
 - 15) Lopata, M. & Onal, E. (1982) Mass loading, sleep apnea, and the pathogenesis of obesity hypoventilation. *Am. Rev. Respir. Dis.*, **126**, 640-645.
 - 16) Moore, L.G., Huang, S.Y., McCullough, R.E., Sampson, J.B., Maher, J.T., Weil, J.V., Alexander, J.K. & Reeves, J.T. (1982) Variable inhibition by falling CO₂ of hypoxic ventilatory response in humans. *J. Appl. Physiol.*, **56**, 207-210.
 - 17) Narkiewicz, K., Van de Borne, P.J.H., Pesek, C.A., Dyken, M.E., Montano, N. & Somers, V.K. (1999) Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation*, **99**, 1183-1189.
 - 18) Okabe, S., Hida, W., Kikuchi, Y., Taguchi, O., Ogawa, H., Mizusawa, H., Miki, H. & Shirato, K. (1995) Role of hypoxia on increased blood pressure in obstructive sleep apnea. *Thorax*, **50**, 28-34.
 - 19) Powell, F.L., Milsom, W.K. & Mitchell, G.S. (1998) Time domains of the hypoxic ventilatory response. *Respir. Physiol.*, **112**, 123-134.
 - 20) Rapoport, D.M., Garay, S.M., Epstein, H. & Goldring, R.M. (1986) Hypercapnia in the obstructive sleep apnea syndrome. *Chest*, **89**, 627-635.
 - 21) Read, D.J.C. (1967) A clinical method for assessing the ventilatory response to carbon dioxide. *Australian. Ann. Med.*, **16**, 20-32.
 - 22) Rebuck, A.S. & Campbell, E.J.M. (1973) A clinical method for assessing the ventilatory response to hypoxia. *Am. Rev. Respir. Dis.*, **109**, 345-350.
 - 23) Rechtschaffen, A. & Kales, A. (1968) A manual of standardized terminology; techniques and scoring system for sleep stages of human subjects. UCLA Brain Information Service/Brain Research Institute, Los Angeles.
 - 24) Sullivan, C.E., Issa, F.G., Berthon-Jones, M. & Eves, L. (1981) Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nares. *Lancet*, **1**, 862-865.
 - 25) Taguchi, O., Hida, W., Okabe, S., Ebihara, S., Ogawa, H., Kikuchi, Y. & Shirato, K. (1997) Improvement of exercise performance with short-term nasal continuous positive airway pressure in patients with obstructive sleep apnea. *Tohoku. J. Exp. Med.*, **183**, 45-53.
 - 26) Verbraecken, J., De Backer, W., Willemsen, M., De Cock, W., Wittesaele, W. & Van de Heyning, P. (1995) Chronic CO₂ drive in patients with obstructive sleep apnea and effect of CPAP. *Respir. Physiol.*, **110**, 279-287.
 - 27) Weil, J.V., Byrne-Quinn, E., Sodal, I.E., Filley, G.F. & Grover, R.F. (1971) Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. *J. Clin. Invest.*, **50**, 186-195.
 - 28) Zwillich, C.W., Sutton, F.D., Pierson, D.J., Creagh, E.M. & Weil, J.V. (1975) Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am. J. Med.*, **59**, 343-348.
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